Amendments to the Specification:

Please replace the paragraph at page 19, lines 1-9, with the following amended paragraph:

Fig. 2C consists of two fusion proteins each composed of a chaperonin subunit 2-times linkage and an antigen protein linked thereto, and four independent chaperonin subunits. The chaperonin-antigen protein complex as shown in Fig. 2D consists of a fusion protein composed of a chaperonin subunit and an antigen protein linked thereto, a fusion protein composed of a chaperonin subunit ~~2~~ 3-times linkage and two antigen proteins respectively linked to the N-terminus and the C-terminus thereof, a fusion protein composed of a chaperonin subunit ~~3~~ 2-times linkage and an antigen protein linked thereto, and two independent chaperonin subunits.

Please replace the text staring at page 22, line 26, to page 23, line 26, with the following amended text:

Now, a method of producing the immunogen of the present invention will be described. The immunogen of the present invention contains a fusion protein composed of an antigen protein and a foldase. In order to produce the fusion protein, a gene encoding the antigen protein and a gene encoding a foldase are linked to produce a fusion gene, and

then the fusion gene is expressed to synthesize the fusion protein. Specifically, a plasmid vector into which the fusion gene is integrated is introduced into a host cell to give a transformant, whereupon the fusion protein is obtained from the extract of the cultured transformant in which the fusion gene is expressed. When the folding factor is a chaperonin, an independent chaperonin subunit and/or a chaperonin subunit linkage may be required in addition to a fusion protein composed of an antigen protein and chaperonin subunits. In these cases, for example, a gene encoding an independent chaperonin subunit and/or a gene encoding a chaperonin subunit linkage may be expressed separately. A plasmid vector into which these genes are introduced may be introduced into a host cell, for example. The fusion gene, and a gene encoding an independent chaperonin subunit and/or a gene encoding a chaperonin subunit linkage may be linked polycistronically on one plasmid vector, or may be introduced respectively into two different plasmids capable of coexistence and replication in one host to co-express in one host. Further, since independent chaperonin subunits naturally occur, a gene encoding a chaperonin subunit on genomic DNA of the host cell may be transcribed and translated to provide chaperonin subunits derived from the host cell. Further, the fusion ~~gene~~ protein, an independent chaperonin subunit, and a chaperonin

subunit linkage may be expressed in different host cells respectively, purified separately, and then mixed. Any antigen protein forms chaperonin-antigen protein complex when being fused with a chaperonin to constitute a fusion protein.

Please replace the text at page 24, lines 13-25, with the following amended text:

Host cells into which the fusion gene or the like is introduced include, but are not particularly limited to, prokaryotes such as bacteria, and yeasts, fungi, plants, insect cells, and mammalian cells. It is more preferable to use bacteria such as Escherichia coli as a host cell because their transformants grow quite rapidly than other host cells with mass production of the fusion proteins or the like. In the case of Escherichia coli as a host cell, the fusion protein may be expressed into its cytosol, or may be expressed and secreted into its periplasm region. In order to express and secrete into its periplasm a fusion protein composed of a folding factor and an antigen protein, a secretion signal sequence region needs to be provided at the ~~5'~~ N-terminus of the fusion protein. Then, the fusion protein is expressed and secreted into the periplasm region because of the existence of the secretion signal sequence.

Please replace the text starting at page 25, line 27, to page 26, line 27, with the following amended text:

Methods of purification of the fusion protein constituting the immunogen of the present invention will be now described. The methods are not particularly limited and may employ conventionally known methods. The following is an example of the methods of purifying a fusion protein composed of an antigen protein and a chaperonin. A transformant in which the fusion protein is expressed is collected and disrupted to recover a cell extract. After the fusion protein in the cell extract is recovered by ammonium sulfate precipitation, the precipitated fraction is dissolved in an appropriate buffer and subjected to ion-exchange chromatography or hydrophobic chromatography to recover fractions containing the fusion protein. The fraction is concentrated by ultrafiltration and subjected to gel filtration using a buffer containing about 5-50 mM magnesium chloride and about 50-300 mM sodium chloride or potassium chloride as a developing solution, whereby a peak just after the exclusion limit is recovered to give the purified fusion protein. In the case of the fusion protein with a tag made of 6-10 histidine residues (hereinafter referred to as "histidine tag") linked to its N- or C-terminus, the fusion protein is purified more easily and efficiently by means of a metal (e.g.

nickel) chelating column. Further, the fusion protein is purified rapidly and easily by immune precipitation or affinity chromatography using an antibody against the chaperonin. However, it is preferable to include ion-exchange chromatography and gel filtration to recover only the fusion protein having a ring structure in the method. In the case of the chaperonin having heat resistance, heat treatment of the extract from the host at 60 to 80°C precipitates and removes the majority of residual proteins derived from the host, thereby purify the fusion protein more simply. Even if the antigen protein itself is not heat-resistant, the ~~fusion~~ antigen protein is not thermally denatured because it is held inside of the chaperonin.

Please replace the text starting at page 30, line 17, to page 31, line 2, with the following amended text:

One of the methods of preparing a desired monoclonal antibody by phage display method is disclosed in Japanese laid-open patent H07-502167. Specifically, a region corresponding to Fab gene is amplified by RT-PCR method using mRNA isolated from an antibody-producing cell of an animal immunized with the fusion protein and primers specific to a region between complementarity determining regions (CDR), and is introduced into a phagemid vector to give an antibody

library maintaining a high degree of diversity. Clones specifically producing Fabs in the presence of helper phages are concentrated and screened using the antigen for immunization, so that a desired Fab is expressed in Escherichia coli in a large amount. After its immunological activity is examined well, its whole-type IgG is expressed in a cultured cell with an expression vector of Fc part gene with which the desired Fab is combined.

Please replace the text at page 37, lines 2-7, with the following amended text:

The harvested cells were suspended in FLAG-binding buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 5 mM ~~MgCl~~ $MgCl_2$, 1 mM EDTA), and then disrupted by sonication. The disrupted cell suspension was centrifuged at 30,000 rpm for 1 hour to give its supernatant that is a soluble fraction. Meanwhile, the same procedure was carried out using Escherichia coli strain BL21(DE3) harboring a vector pTHT1AR for a control experiment.

Please replace the text at page 37, lines 8-19, with the following amended text:

When supernatants and precipitate fractions of the Escherichia coli extracts were analyzed by SDS-PAGE, only from

the soluble fraction of the extracted sample of Escherichia coli cells harboring the expression vector pTrc(GroEL)7□5HT1AR, a band at the position corresponding to the molecular weight of the fusion protein was detected. On the other hand, the antigen proteins were not detected from the soluble fraction of the extract sample of Escherichia coli cells harboring pTHT1AR as a control, although a weak band was detected from the insoluble fraction of the extract sample of Escherichia coli cells harboring pTHT1AR. From these results, it was found that 5-HT1aR ~~gene~~ alone was not expressed in the Escherichia coli soluble fraction, but expressed as a soluble protein when constituting a fusion protein with a GroEL 7-times linkage.

Please replace the text at page 44, lines 2-13, with the following amended text:

When supernatants and precipitate fractions of the Escherichia coli extracts were analyzed by SDS-PAGE, only from the soluble fraction of the extracted sample of Escherichia cells harboring the expression vector pTCP8·5HT1AR, a band at the position corresponding to the molecular weight of the fusion protein was detected. On the other hand, the antigen proteins were not detected from the soluble fraction of the extract sample of Escherichia coli cells harboring pTHT1AR.

From these results, it was found that 5-HT1aR ~~gene~~ alone was not expressed in the Escherichia coli soluble fraction, but expressed as a soluble protein when constituting a fusion protein with a TCPβ 8-times linkage.

Please replace the text starting at page 46, line 29, to page 47, line 12, with the following amended text:

1. Construction of a vector to express a fusion protein with TcFKBP18

The nucleotide sequence of short-type FKBP-type PPIase derived from extremely thermophilic archaeum Thermococcus sp. KS-1 (TcFKBP18) (Ideno et al. Biochem. J. 357, 465-, 2001), which has been known, was shown in SEQ ID No. 14. Oligonucleotides as shown in SEQ ID Nos. 15 and 16 were prepared based on the information of this nucleotide sequence. PCR using a plasmid pEFE1-3 (Iida et al., Gene, 222, 249-, 1998) containing TcFKBP18 gene as a template and oligonucleotides as shown in SEQ ID Nos. 15 and 16 as a primer set was carried out, whereby a DNA fragment containing TcFKBP18 gene was amplified. Herein, an NcoI site and an SpeI site derived from the primers were introduced into each terminus of the amplified DNA fragment. The amplified DNA fragment was introduced into pT7BlueT vector by TA cloning. The nucleotide sequence of the introduced DNA fragment was

determined, and confirmed to be the same as the nucleotide sequence as shown in SEQ ID No. 14.